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Tonic Spasms in Multiple Sclerosis
Anatomic Basis and Treatment

LAWRENCE S. HONIG, MD, PhD
PHILIP H. WASSERSTEIN, MD
Stanford, California

BRUCE T. ADORNATO, MD
Palo Alto, California

TONIC SPASMS are among several paroxysmal symptoms of multiple sclerosis. Although first described decades ago, they are frequently misdiagnosed, and they have not been well localized. We present the case of a 31-year-old man with the sole complaint of stereotyped, left-sided, painful tonic spasms primarily affecting the arm, with less involvement of leg and face. Hyperventilation reliably precipitated the spasms.

Report of a Case

The patient, a 31-year-old right-handed man, was seen because for six weeks he had had intermittent "muscle spasms" involving the left side of his body. They typically began in the left shoulder and progressed distally to the arm, hand, and fingers. There was simultaneous involvement of his left hip and leg. The feeling of muscle tension was accompanied by uncontrollable shaking and spasmodic movements of the affected parts, with the fingers "going every which way automatically." In addition, a pins-and-needles tingling sensation that was unpleasant and painful developed in the left limbs. The left side of the face was involuntarily drawn up, and he spoke with effort. There was no headache, nausea, vomiting, tinnitus, diplopia, or visual, mental, or sphincteric disturbances preceding or during the attacks, nor were any residual sensory or motor deficits noted.

When these attacks had first started, the patient went to an emergency department. No episodes were witnessed there, and the results of an examination were normal. A diagnosis of "muscle spasm: no neurologic disease" was made, and he was instructed to consult a neurologist should the episodes continue. The episodes were initially only a few seconds in duration and occurred once to three times per day, but over a month's time they increased in severity and frequency, lasting 15 to 60 seconds and occurring as often as three times per hour. While originally benign, they became troublesome to the patient, interfering with his driving and at one point causing him to drop a beverage glass.

His medical history included a period of several months of diplopia at age 12, requiring "visual training classes," but resolving without medical or surgical therapy. He had sustained minor injuries in vehicular accidents, but his only operation was a tonsillectomy at age 7. His habits included two-packs-per-day tobacco smoking and moderate daily alcohol use. No medications or street drugs were being taken.

On general physical examination, no abnormalities were noted. His mental state was notable for anxiety, inappro-

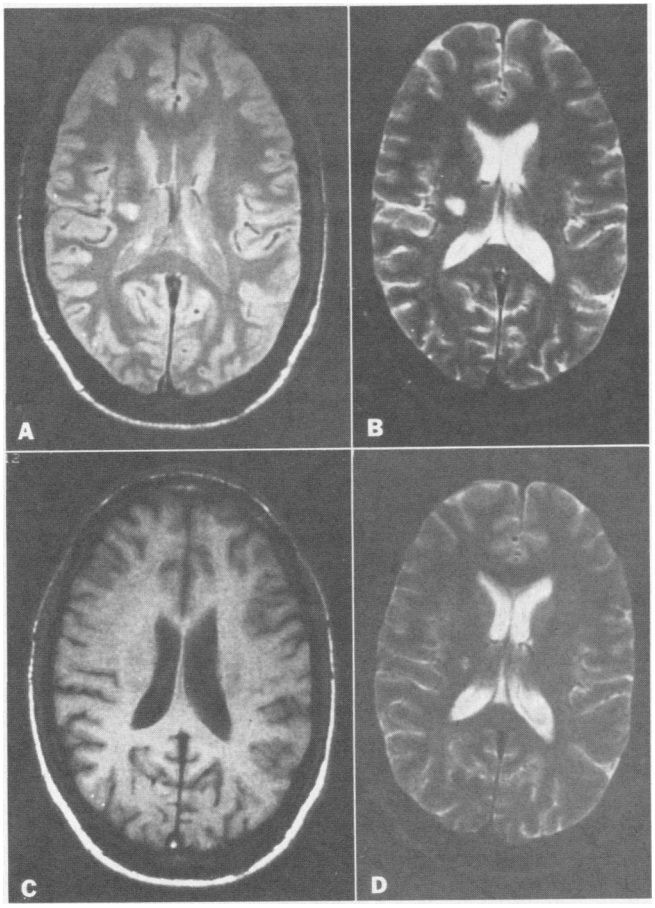

Figure 1.—Brain magnetic resonance imaging: Spin-echo sequences include a proton-weighted first-echo (TR = 2,000, TE = 20 milliseconds) image (**A**) that shows a right internal capsule abnormality with greatly increased signal intensity on a T2-weighted second-echo (TR = 2,000, TE = 80 milliseconds) image (**B**) but no signal abnormality on a T1-weighted (TR = 800, TE = 20 milliseconds) image (**C**). Two months later, the lesion size and signal intensity are decreased, as shown in a T2-weighted image (**D**).

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From the Department of Neurology and Neurological Sciences, Stanford University Medical Center, Stanford, California.

Reprint requests to Lawrence S. Honig, MD, Department of Neurology and Neurological Sciences (H-3160), Stanford University Medical Center, Stanford, CA 94305-5235.

ABBREVIATIONS USED IN TEXT

CSF = cerebrospinal fluid
Ig = immunoglobulin
MRI = magnetic resonance imaging

priate affect, social disinhibition, and increased psychomotor activity. A cranial nerve evaluation, including fundi, elicited entirely normal findings, as did the motor system examination, with normal bulk, tone, strength, gait, and coordination throughout. Sensory testing revealed mild hypesthesia to light touch, pinprick, and vibration on the left hemibody with respect to the midline; proprioception and stereognosis were normal. Muscle stretch reflexes were present and symmetric. No pathologic reflexes were found.

Laboratory studies included normal serum electrolytes, general chemistry panels, urinalysis findings, and hematologic studies, with a sedimentation rate of 2 mm per hour. Serum was negative for fluorescent treponemal antibody absorption, VDRL, fluorescent antinuclear antibody, and rheumatoid factor; serum angiotensin-converting enzyme level, protein electrophoresis, chest roentgenogram, and electrocardiogram were normal. A lumbar puncture yielded clear, colorless cerebrospinal fluid (CSF) with an opening pressure of 150 mm of water. Cell counts were erythrocytes, 10×10^6 per liter, and leukocytes, 13×10^6 per liter, with 0.98 lymphocytes and 0.02 monocytes; the glucose level was 3.4 mmol per liter (61 mg per dl), protein 440 mg per liter, and VDRL negative. A CSF protein analysis by agarose electrophoresis showed a normal albumin level of 168 mg per liter (normal, 130 to 240) and CSF:serum albumin ratio of 0.004 (normal, <0.009), reflecting an intact blood-brain barrier. Elevated levels, however, of immunoglobulin (Ig) G of 72 mg per liter (normal, <55), fraction IgG of 0.164 (normal, <0.105), IgG index of 1.87 (normal, <0.7), and a calculated IgG synthesis rate of 24 mg per day (normal, <3) all suggested central nervous system (intrathecal) immunoglobulin synthesis. The CSF also showed oligoclonal banding, with 2 bands present in the gamma region, without counterparts in the serum.

Hyperventilation for two minutes produced characteristic attacks of left arm flexion and dystonic hand posturing with pain and tremulousness lasting about a minute. The left side of the face also contorted, the head turned to the left, and the left leg tensed.

The electroencephalogram was normal; neither epileptiform activity nor changes in background were seen during or after tonic attacks documented on simultaneous video monitoring. Visual and brain-stem auditory evoked potentials were within normal limits: P100 latencies were 99 milliseconds bilaterally. Somatosensory evoked potentials showed poorly formed P40 cortical responses on stimulation of the left posterior tibial nerve, but they were otherwise normal.

Treatment with carbamazepine (Tegretol), 400 mg per day in divided doses, resulted in the prompt abatement of both spontaneous and hyperventilation-induced spasms. After three months, a trial discontinuation of carbamazepine therapy was pursued and there was no recurrence of attacks off medication. Eight months later, a dense right facial palsy of a lower motor neuron type developed, accompanied by decreased hearing on the right side. This facial paralysis resolved little over the subsequent nine months despite two courses of oral steroid therapy.

At the initial presentation, brain x-ray computed tomography showed a small region of lucency in the posterior limb of the right internal capsule that failed to enhance with intravenous contrast dye. Magnetic resonance imaging (MRI) showed this area, measuring about 2 cm in diameter, as abnormal signal centered in the posterior limb of the right internal capsule extending into adjacent thalamus. The lesion displayed increased signal on the proton-weighted (TR = 2,000, TE = 20 milliseconds) spin-echo image (Figure 1-A), and more intense signal on the T2-weighted (TR = 2,000, TE = 80 milliseconds) image (Figure 1-B), but on a T1-weighted (TR = 800, TE = 20 milliseconds) pulse sequence (Figure 1-C), it possessed normal signal and was not identifiable. Follow-up imaging two months later, when the patient was asymptomatic, showed decreased lesion size and signal intensity on proton (not shown) and T2-weighted (Figure 1-D) images. A third MRI study (no figure) done eight months after the onset of facial palsy, when the patient was without spasms off medical therapy, revealed some further resolution of the capsular abnormality, without the appearance of new lesions.

Discussion

This 31-year-old man had the subacute development of stereotyped, painful tonic spasms involving the left upper extremity and the left side of his face. He had a history of a childhood period of diplopia and a long-standing behavioral disorder. The spasms could be brought on reliably by hyperventilation. When carbamazepine therapy was instituted, both spontaneous and induced attacks disappeared.

The differential diagnosis of stereotyped unilateral body movements without alteration of consciousness includes epileptic seizures, psychogenic attacks, carpopedal spasm (tetany), paroxysmal kinesogenic choreoathetosis, and paroxysmal dystonic choreoathetosis, in addition to the tonic spasms of demyelinating disease. Aside from the fact that this patient's clinical attacks were classic for tonic spasms, none of the other disorders are associated with abnormalities of cerebral white matter. Simple partial epileptic seizures with motor manifestations often show abnormality on ictal scalp electroencephalography. Also, compared with tonic spasms, partial seizures tend to be less frequent, less readily provoked by hyperventilation, and less easily controlled by low doses of carbamazepine. Psychogenic attacks are always a consideration in spells for which objective confirmation is absent, but supportive criteria important for such a diagnosis include nonconformance of the attacks with known disorders, nonphysiologic variability between individual attacks, and some motivational explanation for the occurrence of psychogenic events. Carpopedal spasm (tetany) occurs with hypocalcemia or severe metabolic alkalosis; it is usually painless, bilateral, and longer lasting than a tonic spasm. Paroxysmal kinesogenic choreoathetosis is a rare condition featuring attacks of abnormal motor activity that are brief (seconds to minutes in duration), frequent (as many as 100 per day), and anticonvulsant-responsive. The attacks, however, are commonly induced by sudden movements, tend to be more complex than simple tonic postures, and usually begin at a younger age; also, there is often a family history of such a disorder. Paroxysmal dystonic choreoathetosis is another rare familial disorder. Attacks generally begin in early childhood, last as long as hours at a time, and rarely occur more often than three times a day. The attacks experienced by this patient were

most consistent with the tonic spasms (described later) associated with demyelinating disease.

Multiple sclerosis was ultimately diagnosed in this patient based on the presence of central nervous system lesions separated in time and location, with supportive laboratory (CSF) evidence. While the tonic spasms, the lesion seen by MRI, and the somatosensory potential abnormalities all fit a diagnosis of a single central lesion, additional history included the previous clinical episode of diplopia and a subsequent attack of a dense and unremitting facial palsy. Although this latter lesion was of lower motor neuron type, such facial palsy may occur in multiple sclerosis, presumably from involvement of the intramedullary portion of the seventh cranial nerve root. The MRI signal of the right basal ganglion lesion (Figure 1) was characteristic, although not specific, for a demyelination plaque, as was its subsequent resolution without specific therapy. Cerebrospinal fluid examination showed abnormalities consistent with multiple sclerosis, including mild lymphocytic pleocytosis, elevated central nervous system IgG synthesis, and the presence of oligoclonal IgG bands.

Paroxysmal attacks including dysarthria, ataxia, falling, and tonic spasms are features of multiple sclerosis that are not always recognized as such.[1-19] Tonic attacks are commonly unilateral, with consciousness preserved, and may occur, as in this patient, as the presenting symptom.[2-6] Their nomenclature has not been agreed on and has included tonic spasms,[7] tonic seizures,[2,3,8,10] paroxysmal dystonia,[6] tetanoid attacks,[2,4] and sensorimotor seizures.[10,11] We prefer the term tonic spasms, which is descriptive and distinguishes these white matter phenomena from cortical (epileptic) seizures of grey matter origin. The tonic motor manifestations characteristically are accompanied by paresthesias, are frequently painful,[9,12] last about 30 seconds (range 10 seconds to 3 minutes),[1-12] and may occur repetitively many times per day.[2-4] They are unaccompanied by alteration or loss of consciousness[1-19] or by electroencephalographic epileptiform activity.[2,3,7,9] Tonic spasms frequently show provocative susceptibility to hyperventilation.[2-4,12] Attacks tend to abate spontaneously over months, probably with evolutionary change of the causative demyelinative plaque. Symptomatic treatment with phenytoin has variably shown success[2,3,6,7] or failure,[6,9] but carbamazepine therapy has shown the greatest efficacy in suppressing tonic spasms.[6,7,9,11,14]

Localization within the neuraxis of tonic seizures has been obscure. Some authors have suggested a spinal origin,[9-11] although involvement of the face, as in our patient, argues for a more rostral focus. Others have proposed a brain-stem or subcortical location.[2,15] Pathologic correlations have been few.[7,9] Indeed, Joynt and Green reported that "the location or locations will probably never be satisfactorily fixed because of the diffuse changes found in the nervous system."[3] Nonetheless, the development of x-ray computed tomography provided two reports of imaged single lesions in patients with tonic spasms, albeit in the context of accompanying fixed motor deficits in the affected limbs: a patient with a multiple sclerosis plaque in the internal capsule[19] and another with a putaminal infarct.[20] Our report (previously published in abstract form[21]) is to our knowledge the first of a case in which MRI, a most sensitive technique, was used to show only a single, isolated, demyelinating lesion. This plaque anatomically appears to affect descending corticospinal pathways on the right, correlating with typical tonic seizures in the left (contralateral) body in an otherwise motorically intact person. The lesion involves the posterior limb of the internal capsule, which can account for the face, arm, and leg motor and sensory involvement. Although in this patient the lesion involving the descending corticospinal tract was capsular, presumably other lesions of the pyramidal tract in, for example, the cerebral peduncle or lateral columns of the cord, might result in the same motor symptoms. Although the spinothalamic tract runs in close proximity to the corticospinal tract, the divergent levels of their decussation would seem to demand a supracervical location in those patients in whom pain is ipsilateral to the spasm. Alternatively, ipsilateral pain might not be due to the same primary process involved in the motor activity but to the provoked muscular contraction itself. There have been some cases reported in which sensory symptoms are crossed, being contralateral to the tonic spasms,[9-11,15] and these attacks presumably originate in the spinal cord.

The pathophysiology of tonic seizures might involve spontaneous discharges, ectopic excitation, or ephaptic transmission ("cross-talk") among abnormal (demyelinated) neuronal axons. In some cases, proprioceptive or tactile stimuli have elicited attacks,[7,9,16] perhaps lending support to an ephaptic mechanism. Lhermitte's phenomenon, in which mechanical flexion of the spine causes a paroxysmal sensory abnormality putatively mediated by the dorsal columns, likely represents a fleeting, sensory example of the same excitative phenomenon.[16] Hyperventilation commonly provokes tonic attacks, possibly increasing electrical irritability through vasoconstriction, with relative ischemia and hypoxia[17]; hypocapnia, with accompanying alkalosis; or altered calcium availability from alkalosis.[2,18] Relevant to these mechanisms is the reported suppressive role of acetazolamide.[22] The therapeutic efficacy of the anticonvulsants phenytoin and, particularly, carbamazepine may be related to the abilities of these agents to inhibit repetitive electrical discharges through effects on sodium channel conduction.

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Withdrawal Effects of Metoclopramide

A. MICHAEL NOLL, PhD
Los Angeles, California

DREW PINSKY, MD
South Pasadena, California

METOCLOPRAMIDE HYDROCHLORIDE is a powerful antiemetic that, among other helpful effects on the gastrointestinal tract, also stimulates gastric emptying.[1,2]

We report the case of a woman who took metoclopramide for about six months and experienced subtle adverse reactions. The drug was withdrawn, and the adverse reactions expanded, worsened greatly, and oscillated daily between akinesian (rigid) and akathisian (restless) symptoms. More than a year after the metoclopramide therapy was discontinued, the patient still shows adverse effects of the drug.

Report of a Case

Background

The patient, a 41-year old woman, was diagnosed by endoscopy as suffering from an ulcer. She was placed on a regimen of sucralfate (Carafate), 4 grams per day (four times a day), and metoclopramide hydrochloride (Reglan) at an initial dosage of 20 mg per day (four times a day) by her gastroenterologist. Two months later, the metoclopramide dosage was increased to 40 mg per day (four times a day).

About a month after the metoclopramide therapy was started, the patient had a weak menses. The next menses on day 30 was "short and spotty" according to the patient and was then followed by the complete cessation of menses. At that time, this problem was thought to be the result of a possible postconcussion syndrome from a recent head trauma that had occurred a few weeks after the metoclopramide regimen was started. The patient had been using crutches as a result of a knee operation, fell on a flight of stairs, hit her head, and lost consciousness. In retrospect, the metoclopramide was the most likely cause of the amenorrhea because it is well known to elevate serum prolactin levels, which would then halt the menses. Furthermore, the patient appeared to be recovering from the concussion.

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Dr Noll is with the Annenberg School for Communication, University of Southern California, Los Angeles. Dr Pinsky is in private practice in South Pasadena, California.

Reprint requests to A. Michael Noll, PhD, Annenberg School for Communication, University of Southern California, Los Angeles, CA 90089-0281.

Adverse Reaction

About five months after the initial use of the metoclopramide, a variety of subtle symptoms became apparent, in addition to the continuing amenorrhea. These symptoms were somewhat episodic and included trembling of the hands and legs, an inability to sit still, complaints of difficulty in thinking clearly, staring blankly with diminished blinking, a greatly reduced libido, sweaty palms, and a feeling of warmth. The patient complained of feeling anxious, and sustained resting tachycardia developed. Because metoclopramide causes nearly identical adverse reactions, withdrawal was initiated.

Withdrawal Syndrome

The metoclopramide was withdrawn with an immediate decrease to 10 mg per day followed ten days later by a complete withdrawal. Just before the initiation of the graduated withdrawal, the patient's serum prolactin level, measured in a blood specimen drawn in the morning, was 139 μg per liter (normal < 20).

During the ten-day withdrawal period, many of the previously noted adverse reactions worsened. In addition, the patient reported nausea, galactorrhea, and frequent urination of modest volumes. The patient's palms and soles were sweaty, and a rigidity appeared, particularly in the hands.

After the complete withdrawal of the metoclopramide, her symptoms worsened greatly and some new symptoms appeared, such as a crawling sensation on the arms (dysesthesia). The only improvement was in the serum prolactin level, which, measured two weeks after the withdrawal began, had returned to normal levels at 11 μg per liter. This confirmed our belief that the metoclopramide therapy, and not a postconcussion syndrome, was the cause of the amenorrhea.

After an initial period of about a week after complete withdrawal, a number of the withdrawal symptoms appeared to fall into two separate groups.* All symptoms disappeared during sleep. The patient frequently complained of difficulty concentrating and showed signs of depression.

The first group of symptoms consisted of features such as muscle tightness and rigidity, blank staring with a masklike facies, diminished blinking and dysphagia, jerky voluntary movement of the hands and arms, and a slight tremor at rest. Motor activity was severely decreased and bradykinetic, associated with a vocal apraxia. The patient complained of feeling warm, her palms were sweaty, and her skin temperature was elevated, but there was no fever. This group of symptoms will be called the rigid, or akinesian, set.

These features are all parkinsonian in nature and would appear to be associated with secondary parkinsonism.[3(p1422)] Noteworthy, however, is that such classic Parkinson's disease features as a "pill-rolling" movement of the fingers and "cogwheel" rigidity were absent.

The second group of symptoms consisted of such features as restlessness and agitation, foot tapping, pacing, involuntary choreiform movements with hemiballismus, and rocking and swaying of the upper body. This second group of symptoms is associated with motor restlessness (akathisia) and hence will be called the restless, or akathisian, set.[4] Many of these features are associated with tardive dyskine-

*The patient assisted in this report by keeping careful records of the details of her withdrawal symptoms.